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Hyponatraemia associated with lopinavir–ritonavir?

Hyponatraemia is an unusual complication of treatment with highly active antiretroviral therapy (HAART) and to our knowledge has not been reported in association with the use of lopinavir–ritonavir in adults.[1] Common to the protease inhibitor class of antiretrovirals, the important well-recognized side effects of lopinavir–ritonavir include hepatic dysfunction, diabetes, and lipodystrophy syndrome with an increased risk of pancreatitis.[2]

A 42-year old Zimbabwean man presented in July 2005 with confusion, headaches, blurring of vision, myalgia, dysphagia, and weight loss. He was noted to have oesophagopharyngeal candidiasis, bilateral uveitis, and was confused with an expressive dysphasia. HIV serology was positive with a CD4 count of 30 cells/μL and HIV viral load of 380 847 copies/mL. MRI of the head demonstrated symmetrical white matter changes throughout the hemispheres in keeping with an HIV dementia. CSF sampling showed 10 lymphocytes, 0 polymorphs, no organisms on Gram stain, glucose 4.5 mmol/L (serum 8.9 mmol/L), and protein 0.69 g/L. CSF PCR for herpes simplex virus, varicella-zoster virus, enterovirus, mycobacteria, and JC virus was negative as was cryptococcal antigen and mycobacterial culture. Toxoplasma and syphilis serology was negative and cytomegalovirus viral load in blood was <50 copies/mL. An EEG was normal. He was treated with fluconazole 200 mg once daily, co-trimoxazole 960 mg three times per week, and topical cyclopentolate (1%), dexamethasone (0.1%), and timolol (0.25%) for uveitis. Subsequently he was commenced on HAART with lamivudine 150 mg twice daily, tenofovir 245 mg once daily and lopinavir–ritonavir three tablets twice daily. Blood biochemistry demonstrated a mild hepatitis with a transient rise in ALT to 184 IU/L prior to the introduction of HAART and probably secondary to fluconazole. After five days of HAART he was discharged with a declining ALT and plasma sodium of 133 mmol/L having been within the normal range (135–145 mmol/L) on admission.

Two days later he was readmitted with worsening confusion. He was clinically euvolemic and had a Glasgow coma score (GCS) of 14/15. Investigations showed that cranial imaging was unchanged but there was marked derangement in electrolytes with a serum sodium of 111 mmol/L, potassium 4.8 mmol/L, urea 5.4 mmol/L, and creatinine 80 mmol/L. Urine analysis was negative for protein, blood, nitrites, and leukocytes. During the first five days of admission, the paired urine and plasma osmolality ranged between 330 and 732 mOsm/kg and between 239 and 255 mOsm/kg, respectively. The patient had a raised urine sodium of 76 mmol/L. The low plasma osmolality, raised urine osmolality, and raised urine sodium indicated a syndrome of inappropriate secretion of antidiuretic hormone (SIADH). Repeat CSF sampling was acellular, glucose 2.3 mmol/L (serum glucose 4.9 mmol/L), and protein 0.34 mmol/L. He was treated for SIADH by fluid restriction and HAART was discontinued since temporally this was the most likely cause. Investigations to identify an alternative etiology were negative including thyroid function, synacthen test (serum cortisol response to intramuscular tetracosactide) for adrenal insufficiency, chest X-ray, and a septic screen. EEG demonstrated intermittent bursts of a partial seizure pattern. Anticonvulsant therapy with sodium valproate was commenced. Over six days the serum sodium returned to normal. HAART was reintroduced with lamivudine 150 mg twice daily, tenofovir 245 mg once daily, and atazanavir–ritonavir. Electrolytes remained normal and subsequently tenofovir was substituted with abacavir, since the latter has greater CNS penetration and may be beneficial in the setting of HIV dementia.[3,4]

Use of lopinavir–ritonavir is set to rise as clinical trials suggest superior clinical efficacy, no known de novo resistance in treatment-naïve individuals, and a reported side-effect profile to date that is favorable.[5,6] Since the only change in the second HAART regimen was a switch from lopinavir to atazanavir, this report indicates that lopinavir was the most likely cause of the abrupt drop in sodium when using lopinavir boosted with ritonavir. Normal urine analysis did not suggest any direct tubular damage. Drugs used in the management of HIV-related infections are known to precipitate hyponatraemia through an SIADH effect (pyrazinamide, ethambutol),[7] an amiloride-like effect on the renal tubules (high dose trimethoprim),[8] or by as yet undefined mechanisms (amphotericin B, pentamidine).[8] HAART-associated hyponatremia is rare and described only with zalcitabine (Roche® product information) and lopinavir–ritonavir in children.[1] Laboratory investigations indicate that induction

of SIADH by lopinavir was probably responsible for the severe hyponatraemia in our patient.

Conflict of interest: No conflict of interest to declare.

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Antimicrobial resistance of *Pseudomonas aeruginosa* in pediatric infections

Problems encountered in the management of pediatric infections include treatment failure, which often occurs as a result of antimicrobial-resistant bacterial strains; especially among *Pseudomonas aeruginosa*.[1,2] For this reason antimicrobial drug activity surveillance is necessary, especially for opportunistic and nosocomial *P. aeruginosa*.[2]

In Latin America, resistant bacteria are emerging as a real threat in the community as well as in hospital-acquired infections, including pediatric infections.[2] We reviewed susceptibility data of isolates cultured from hospitalized pediatric patients with suspected community-acquired infections in the West General Hospital (WGH) Caracas, Venezuela between 1997 and 2003. The WGH is a 300-bed general community hospital serving people from west Caracas. Samples were taken before antimicrobial drug therapy was commenced. Samples were processed and organisms identified by traditional methods. In vitro antimicrobial susceptibility of the isolates was assessed by an agar disk diffusion method using Mueller–Hinton agar as recommended by the Clinical and Laboratory Standards Institute (formerly NCCLS). Antipseudomonal third generation cephalosporins and carbapenems are freely prescribed in hospitalized patients but previous antimicrobial drug exposure in this patient series was not measured; there were no chronic conditions reported.

During this seven-year period, *P. aeruginosa* accounted for 137 (4%) of 3425 bacterial isolates from children: 49% from otorrhinolaryngological (ORL) infections, 18% urinary tract infections, 7% skin, and 7% gastrointestinal tract, among others. Overall susceptibility rates are shown in Figure 1. Better antimicrobial activity was observed with ciprofloxacin, meropenem, and imipenem (<5% resistant) than for gentamycin, piperacillin and piperacillin/tazobactam (>10% resistant). For urinary isolates, we found strains resistant to norfloxacin (13%) and gentamycin (8%), but only intermediate resistance to aztreonam, ceftazidime, and ciprofloxacin (8% for each). Susceptibility to imipenem, piperacillin/tazobactam, and tobramycin was 100%. In ORL infections, we found significant resistance to carbenicillin (18%) and some resistance to meropenem (5%) and imipenem (3%) but 100% susceptibility to ciprofloxacin, ofloxacin, and piperacillin/tazobactam.

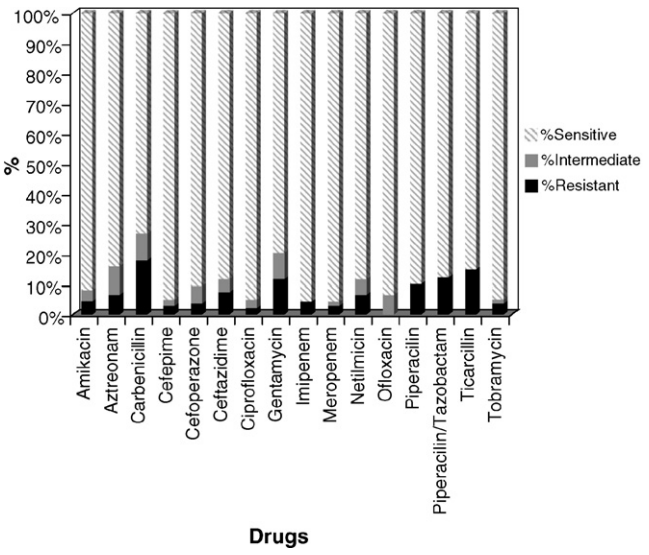

Figure 1 Overall antimicrobial drug susceptibility (%) of *Pseudomonas aeruginosa* isolated from pediatric infections against tested antibiotics (WGH, Venezuela, 1997–2003).